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EXAMINER

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**BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES**

Paper No. 24

Application Number: 09/066,255
Filing Date: April 23, 1998
Appellant(s): Buechler et al

Michael A. Whittaker
For Appellant

MAILED
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EXAMINER'S ANSWER

This is in response to appellant's brief on appeal filed May 13, 2002.

(1) *Real Party in Interest*

A statement identifying the real party in interest is contained in the brief.

(2) *Related Appeals and Interferences*

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) *Status of Claims*

The statement of the status of the claims contained in the brief is correct. However, it is noted that this application still contains claims 23-27, 29, 31, 33 and 35 that have been withdrawn from consideration as not directed to the elected invention.

(4) *Status of Amendments After Final*

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) *Summary of Invention*

The summary of invention contained in the brief is correct.

(6) *Issues*

The appellant's statement of the issues in the brief is correct.

(7) *Grouping of Claims*

Appellant's brief includes a statement that claims 28, 30, 32 and 34 stand or fall together.

(8) *Claims Appealed*

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) *Prior Art of Record*

The following is a listing of the prior art of record relied upon in the rejection of claims under appeal.

5,135,717	Renzone et al	8-1992
4,434,236	Freytag et al	2-1984
4,803,170	Stanton et al	2-1989

Margaron et al. "Photodynamic properties of naphthosulfobenzoporphyrines, novel asymmetric, amphiphilic phthalocyanine derivatives." J. Photochem. Photobiol. B: Biol., Vol. 14, (1992), pp. 187-199.

(10) *Grounds of Rejection*

The following ground(s) of rejection are applicable to the appealed claims:

(1) Claims 28, 30, 32 and 34 are rejected under 35 U.S.C. 112, second paragraph. This rejection (from prior Office action, Paper No. 12) is set forth below:

Claims 28, 30, 32 and 34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims contain the term "ligand analogue", which is deemed to be indefinite. It is not clear what are the similarities and differences between the ligand and the ligand analogue; that is, how "analogous" must these two compounds be? Thus, it is impossible to determine the metes and bounds of the invention and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

(2) Claims 30 and 34 are rejected under 35 U.S.C. 103. This rejection (from prior Office action, Paper No. 12) is set forth below:

Claims 30 and 34 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Margaron et al (J. Photochem. Photobiol. B 1992-on PTO-1449, Paper No. 8) in view of Renzoni et al (US 5,135,717) further in view of Freytag (US 4,434,236).

Margaron et al teach water-soluble hybrid phthalocyanine derivatives (see Figure 1). The compounds taught by the reference consist of phthalocyanines where at least two of the four pyrrole moieties comprise a different number of rings (see in Figure 1, compounds labeled M-N₂SB₂P (cis and trans)). The photodynamic properties of the compounds are studied in biological systems (see Abstract). The compounds have superior absorption properties due to "the perturbation of the (na)phthalocyanine D_{4h} symmetry and the modification of the acennalation" (see page 188, 1st two

paragraphs). Margaron et al lacks the teaching of using these compounds in a conjugate.

However, use of phthalocyanine derivatives in conjugates was well known in the art at the time of filing. Renzoni et al teach water-soluble phthalocyanine derivatives (see column 3, lines 29-55) that read directly on those of the instant claims. These phthalocyanines are conjugated to biologically active agents such as antibodies (column 39, lines 1-25), peptides or nucleotides (see claim 3 of the reference). The conjugates can be used in biological assays (see Example 16, column 39). The Renzoni reference lacks the specific teaching of a competitive assay as recited in the claims.

However, one of ordinary skill in the art would know that such labeled antibodies could be used in a competitive assay, because such assays were very well known in the art at the time of filing. For example, Freytag teaches an assay that is the same as the one claimed, except for the fact that Freytag uses different labels for the antibodies than the ones of the instant claims (see Abstract, Examples and claims 1-7 of the reference). However, Freytag does discuss that fluorophores can be used for labeling the antibodies (column 3, lines 43-48).

Therefore it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use the water-soluble hybrid phthalocyanine derivatives of Margaron et al in a conjugate, as taught by Renzoni et al, and to further use these compounds as the fluorescent tags in the method of Freytag. A person of ordinary skill in the art would have been motivated to make such a substitution to use a

fluorophore with “more ideal spectral properties” as taught by Renzoni et al (column 1, lines 49-52); specifically, the fluorophore of Margaron et al would have preferable properties based on its asymmetry.

(3) Claims 28 and 32 are rejected under 35 U.S.C. 103. This rejection (from prior Office action, Paper No. 12) is set forth below:

Claims 28 and 32 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Margaron et al (J. Photochem. Photobiol. B 1992-on PTO-1449, Paper No. 8) in view of Renzoni et al (US 5,135,717) and further in view of Freytag (US 4,434,236) as applied to claims 30 and 34 above, and further in view of Stanton et al (US 4,803,170).

The teachings of Margaron et al concerning water-soluble hybrid phthalocyanine derivatives are set forth *supra*. Also, the combination of Renzoni et al and Freytag teach that water-soluble phthalocyanine derivatives conjugated to biomolecules can be used in a competitive assay, as discussed *supra*. None of these references discloses the configuration of bound ligand analogue in step b (claim 28) and furthermore the prior binding to a solid phase (claim 32) recited in the instant claims.

However, one of ordinary skill in the art would know that such a configuration could be easily achieved, and would simply be a design choice in the creation of the assay set-up. Such assays were well known in the art at the time of filing. For example, Stanton et al discusses a competitive assay where the analyte conjugate and ligand/marker binding partner are both bound to a solid phase (Abstract and column 3).

Most importantly, “excess analyte conjugate becomes sequestered...on a surface, where its marker activity can be read as an indication of analyte presence” (column 3, line 66 – column 4, line 1).

Therefore it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use the water-soluble hybrid phthalocyanine derivatives of Margaron et al in a conjugate, as taught by Renzoni et al, and to further use these compounds as the fluorescent tags in the method of Freytag. A person of ordinary skill in the art would have been motivated to make such a substitution to use a fluorophore with “more ideal spectral properties” as taught by Renzoni et al (column 1, lines 49-52); specifically, the fluorophore of Margaron et al would have preferable properties based on its asymmetry. One would be additionally motivated to use the bound configuration of Stanton et al to create a more facile assay, as taught by the reference (column 1, lines 9-18).

(11) Response to Argument

35 U.S.C. 112, second paragraph

Appellants argue that “ligand analogue” is definite (Brief, pages 12-15). However, the examiner maintains that this term makes it impossible to determine the metes and bounds of the invention. Appellants cite a dictionary which states the definition of “analogue” to be a “chemical compound that is structurally similar to another but differs slightly in composition” (Brief, page 13). The question at hand is not what the term means but the fact that it is a

relative term. This terminology simply does not provide a standard for ascertaining the requisite degree of “analogy” applicant intends. It is unclear how “analogous” two compounds must be to be considered “analogues” of each other.

Appellants also argue that they have “explicitly defined the phrase “ligand analogue” to refer to molecules that are capable of binding to a binding partner (i.e. ligand receptor) for a target ligand, but that may differ slightly in composition from the target ligand” (Brief, page 15). The examiner maintains that this is not sufficient to clearly delineate the similarities and differences between the ligand and the ligand analogue and that the phrase renders the claim indefinite. How different (or similar) must the two compounds be to be considered as differing “slightly in composition”?

It is also noted that although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Further, with respect to appellants citation of other issued US patents that use this terminology (Brief, page 14), it is well settled that whether similar claims have been allowed to others is immaterial. See *In re Giolito*, 530 F.2d 397, 188 USPQ 645 (1976). The examiner maintains that *in the instant case*, the use of the term “ligand analogue” is deemed to be indefinite.

35 U.S.C. 103

It is noted that appellants have addressed the two rejections under 35 U.S.C. 103 in a single argument (see Brief, page 9, paragraph 2). Thus, the examiner will address the arguments in the same manner below.

Appellants argue that there is no motivation to combine the references, specifically because the cited Margaron et al reference is directed to phototherapy and that “the “superior properties” of water soluble hybrid phthalocyanine derivatives on which the Examiner relies to combine the cited references fail to provide a motivation to provide the instantly claimed methods” (Brief, page 16). Appellants cite both of the advantages that are relied upon by the examiner (Brief, pages 17-18) and state that because there is nothing that would indicate that the water soluble hybrid phthalocyanine derivatives would have any utility as a label (as in the instant claims).

The examiner respectfully disagrees. In response to appellants’ arguments, it is noted that the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). As discussed in the rejection, the examiner’s position is that the *combined* teachings of the references render appellants’ invention prima facie obvious to one of ordinary skill.

Specifically, in appellants’ discussion of the Margaron et al reference with respect to the use of phthalocyanine derivatives in cancer phototherapy, appellants appear to imply that this reference is non-analogous art. However, it has been held that a prior art reference must either be in the field of applicant’s endeavor or, if not, then be reasonably pertinent to the particular problem with which the applicant was concerned, in order to be relied upon as a

basis for rejection of the claimed invention. See *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992). In this case, the teaching of phthalocyanine derivatives for phototherapy (i.e. uptake in cells) is pertinent to the problem of using labels in a biological assay as both involve binding of a labeled compound to a target and absorption properties of such labels. "A reference is reasonably pertinent if, even though it may be in a different field from that of the inventor's endeavor, it is one which, because of the matter with which it deals, logically would have commended itself to an inventor's attention in considering his problem."; *In re Clay*, 966 F.2d 656, 659, 23 USPQ2d 1058, 1060-61 (Fed. Cir. 1992) and *Wang Laboratories Inc. v. Toshiba Corp.*, 993 F.2d 858, 26 USPQ2d 1767 (Fed. Cir. 1993).

Although appellants are correct in stating that Margaron et al teach that their phthalocyanine derivatives are useful because they can readily absorb light toward the red end of the physical spectrum, thus allowing the use of a light wavelength that penetrates deeper into tissue (Brief, page 17), the full teachings of Margaron et al should be considered.

Consider the following from Margaron et al (page 187 bottom through page 188, top):

"The rationale for the latter [molecules that absorb more strongly towards the red end of the spectrum] is that light above 680 nm allows for deeper penetration into biological tissues *as well as the availability of less expensive and more reliable light sources at these higher wavelengths*" (emphasis added)

Thus, Margaron et al teach two advantages for absorbing toward the red end of the spectrum.

It was well known in the art at the time of filing that absorbing toward the red end of the spectrum is advantageous because low cost semiconductor lasers can be used (see additionally, Renzoni et al columns 1-2). Thus, the use of the phthalocyanine derivatives of Margaron et al

as labels in a conjugate (as taught by Renzoni et al) would be obvious to make use of such advantages.

Note, the strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. *In re Sernaker*, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983). In the instant case, the beneficial result of the combination of references is being able to use “a less expensive and more reliable light source” as taught by Margaron et al.

Appellants argue that the examiner’s comparison of the structural similarity of the compounds of Margaron et al and Renzoni et al and the substitution of one structurally similar compound for another “would lack both a motivation and a reasonable expectation of success in combining the cited references” (Brief, pages 18-20). Appellants also argue that the “the mere fact that one type of molecule may be used as both a photosynthesizer and a label would not lead the skilled artisan to believe that all photosynthesizers would make a useful label” (Brief, page 19). The examiner’s position is as follows. Margaron et al **does** teach the absorption maxima (which is related to fluorescence) for hybrid phthalocyanine derivatives that read on those claimed. Also, the compounds of the Margaron reference meet **all** of the limitations of the “water-soluble hybrid phthalocyanine derivatives” of the claims and thus would have the same properties of such compounds. Fluorescence is a property that depends on the physical structure of a compound and thus would be an intrinsic property of the

molecule itself. Also, it is well known in the art that phthalocyanine derivatives are fluorescent, see teachings of Renzoni et al for example.

The Renzoni reference teaches that absorbing toward the red end of the spectrum is advantageous because low cost semiconductor lasers can be used (see columns 1-2 of Renzoni et al, especially column 1, lines 39-45 and column 2, lines 1-3). Margaron et al also contains such teachings (see above). Thus, using molecules that absorb at such wavelengths would be obvious and Margaron et al teach such compounds. Again, Margaron et al teach “hybrid phthalocyanine derivatives” that meet **all** of the limitations of the instant claims and thus these compounds would have the same properties of the claimed compounds. Also, Renzoni et al teach the use of water-soluble phthalocyanine derivatives as fluorescent labels in conjugates. The examiner recognizes that the phthalocyanine derivatives of Renzoni et al are not “hybrid phthalocyanine derivatives” as instantly defined; however, they possess a high degree of structural similarity to those claimed. As stated above, the motivation to use the “hybrid phthalocyanine derivatives” of Margaron et al in the conjugates of Renzoni et al is to achieve the beneficial result of being able to use “a less expensive and more reliable light source” as taught by both Margaron et al and Renzoni et al.

Appellants state that the other cited references do not “cure the flaws in the Examiner’s faulty prima facie case” (Brief, page 20). As stated in the rejections (reproduced above) these references (Freytag and Stanton) are cited to demonstrate that the claimed assay steps are well known in the art; consider the following:

...Freytag teaches an assay that is the same as the one claimed, except for the fact that Freytag uses different labels for the antibodies than the ones of the instant claims (see Abstract,

Examples and claims 1-7 of the reference). However, Freytag does discuss that fluorophores can be used for labeling the antibodies (column 3, lines 43-48).

...Stanton et al discusses a competitive assay where the analyte conjugate and ligand/marker binding partner are both bound to a solid phase (Abstract and column 3). Most importantly, "excess analyte conjugate becomes sequestered...on a surface, where its marker activity can be read as an indication of analyte presence" (column 3, line 66 – column 4, line 1).

Appellants go on to argue that statements made by the Examiner with respect to the fluorescent properties not being claimed "ignores the requirements of the ...asserted prima facie case" (Brief, page 21). These statements are reproduced below:

Further, "the fluorescence properties of such phthalocyanine derivatives" are *not being claimed*. There is nothing in the instant claims with respect to a specific stokes shift and/or intensity or any other particulars of the fluorescence of the molecule. In fact, there is nothing in the instant claims that limits them to fluorescence at all. The claims merely state "generating a detectable signal". Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

The examiner made this point in answer to appellants previous arguments regarding various fluorescent properties and the "superior properties of the instant invention" claimed by appellant, which are discussed further below (paragraph after next).

With respect to appellants' argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning (Brief, page 22), it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re*

McLaughlin, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). The examiner maintains that the combined teachings of the cited references indicate information that was within the level of ordinary skill and render the claimed invention prima facie obvious.

Lastly, appellants refer again to the “superior properties of the instant invention” stating that “the water-soluble phthalocyanine derivatives of the instantly claimed methods exhibit advantageously large stokes shifts and intensities” (Brief, page 23). It appears as if appellants may be trying to imply that the claimed method produces unexpected results. As stated previously by the examiner (in the final Office Action, Paper No. 12), objective evidence which must be factually supported by an appropriate affidavit or declaration to be of probative value includes evidence of unexpected results... See, for example, *In re De Blauwe*, 736 F.2d 699, 705, 222 USPQ 191, 196 (Fed. Cir. 1984) (“It is well settled that unexpected results must be established by factual evidence”). This evidence has not been provided in the prosecution of the instant case. Appellants refer to the instant specification with respect to the stokes shifts of certain water-soluble phthalocyanine derivatives; however, no *specific* water-soluble phthalocyanine derivative is instantly claimed (i.e. by specific structure).

Moreover, any differences between the claimed invention and the prior art may be expected to result in some differences in properties. The issue is whether the properties differ to such an extent that the difference is really unexpected. *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986) (In MPEP § 716.02). The examiner maintains that any differences between the claimed water-soluble phthalocyanine derivatives and the water-soluble phthalocyanine derivatives of Margaron et al would be predictable to one of ordinary skill

considering the state of the art concerning phthalocyanine derivatives (and the use of such as labels in assays, e.g. Renzoni et al).

For the above reasons, it is believed that the rejections should be sustained.

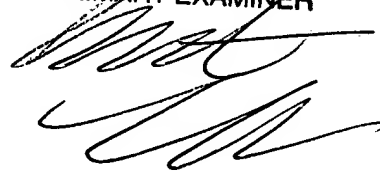
Respectfully submitted,



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